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REVIEW

Anorexia Nervosa and Osteoporosis

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Abstract
Patients with anorexia nervosa (AN) often experience low bone mineral density (BMD) and increased fracture risk, with low body weight and decreased gonadal function being the strongest predictors of the observed bone mineral deficit and fractures. Other metabolic disturbances have also been linked to bone loss in this group of patients, including growth hormone resistance, low insulin-like growth factor-1 (IGF-1) concentrations, low leptin concentrations, and hypercortisolemia. However, these correlations lack definitive evidence of causality. Weight restoration and resumption of menstrual function have the strongest impact on increasing BMD. Other potential treatment options include bisphosphonates and teriparatide, supported by data from small clinical trials, but these agents are not approved for the treatment of low BMD in adolescents or premenopausal women with AN.

Keywords Anorexia nervosa · Osteoporosis · Fracture

Introduction

Anorexia nervosa (AN) is a disorder characterized by severe fear of weight gain, food restriction, and pathologically low body weight and is often associated with decreased bone mineral density (BMD) and an increased risk of fractures. These alterations in bone health are believed to be due to caloric restriction, malnutrition, and possibly associated hormonal abnormalities.

This review article will explore the prevalence and pathophysiology of osteoporosis and fractures in patients with AN, as well as published observations and studies on treatment.

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Anorexia Nervosa and Bone Mineral Density

It is estimated that up to 50% of patients with active AN have Z or T scores < -2 on Dual Energy X-Ray Absorptiometry (DXA) and that more than 90% have T scores ≤ -1 [1, 2], with a recent meta-analysis reporting 0.16 kg lower whole-body mineral content in patient with active AN compared to controls [3]. Since AN is more prevalent in females, most of the published studies on AN-related bone disease are in women and female adolescents. However, low BMD has also been found in adolescent boys at rates similar to adolescent girls [4, 5] and in 60–80% of men with AN [6, 7]. Interestingly, the severity of AN-related low BMD may differ between patients with restricting (AN-R) and binge-purge (AN-BP) disease, possibly related to differences in body weight between the two groups as we will discuss later. Patients with AN-R have a higher prevalence of osteoporosis (defined as a Z score < -2.0 or T score < -2.5) than osteopenia (defined as a Z score between -1.0 and -2.0 or T score between -1.0 and -2.5), while patients with AN-BP are more likely to have osteopenia than osteoporosis ($p < 0.01$) [8].

In adults with AN, this bone mineral deficit is believed to be due to increased bone resorption and decreased bone formation that are triggered by some of the physiologic and hormonal factors that will be discussed later in this article. Adolescents with AN have been consistently shown to have

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suppressed bone formation, likely leading to low peak bone mass [9–12].

Anorexia Nervosa and Fracture Risk

AN is associated with a significant increase in fracture risk, with up to a threefold increase in the lifetime risk of fractures [13]. This association has been best studied in women and it has been estimated that up to 57% of women with AN will experience at least 1 fracture in their lifetime, a risk that starts shortly after disease onset and that lasts through the duration of the disease and possibly beyond, with increased risk of fracture reported as late as 38 years after the diagnosis of AN [13–16]. In a recent analysis, Frølich et al. found a fracture incidence rate ratio (IRR) of 2.2 (99% CI 1.6–3.0) in 803 female patients with AN from the Danish National Registry. Of particular concern was the very high IRR of hip fractures which reached 6.6 (99% CI 2.6–18.0). This excess fracture risk persisted (albeit lower) in patients whose AN was in remission (IRR 1.7, 99% CI 1.1–2.7), as defined by an ideal body weight > 85% and no purging episodes within 6 months. Age of onset of AN, duration of disease before presentation, and nadir body mass index (BMI) were identified as predictors of fracture risk ($p < 0.05$) [17]. Only one study has assessed fracture risk in men with AN and found it to be increased only after the age of 40 years, while women experienced increased risk at all age groups [18].

While low BMD as measured by DXA is a well-documented predictor of fracture risk in the general population [19], this relationship has not been confirmed in patients with AN. More specifically, a recent prospective cohort study compared 145 patients with AN with an average age of 36 years to age- and sex-matched controls. AN was associated with a higher risk of fracture compared to controls (13/1000 patient-years vs 6.6/1000 patient-years, $p < 0.05$), but the study failed to demonstrate a correlation between fracture risk and BMD despite a mean follow-up period of 18.6 years [2]. Likewise, two cross-sectional studies could not detect a correlation between BMD and fracture risk in adolescent girls and women with AN [16, 20]. These observations raise the question of whether modalities other than DXA should be used to predict fracture risk in young women with AN.

Alternative Techniques for Evaluation of Bone Microarchitecture and Strength

High-resolution peripheral quantitative CT (HR-pQCT) has been used to assess bone architecture and estimate bone strength in patients with AN. Decreased total and trabecular volumetric BMD (vBMD), increased cortical porosity and trabecular separation, and decreased bone strength have been noted at the distal radius in adolescent girls with AN [21]. At the distal tibia in adolescent girls and young women with AN, decreased total and cortical vBMD, increased cortical porosity, and decreased cortical thickness, trabecular number, and estimated strength were also described [22]. In a study of 25 young women with AN that concomitantly assessed the distal radius and tibia, Frølich found low estimated failure loads at both sites, but total vBMD was decreased at the distal tibia only. All indices of trabecular microarchitecture (bone volume/tissue volume, trabecular thickness, trabecular number, and trabecular spacing) were impaired at the distal tibia, with more variability seen at the distal radius, with impaired bone volume/tissue volume, trabecular number, and trabecular spacing but no difference in trabecular thickness compared to controls [23]. While this novel technology may provide insight into bone strength, larger scale studies with correlations to fracture risk in patients with AN will be very important to inform its clinical utility.

In recent years, bone marrow adiposity (BMA), measured by single-voxel proton magnetic resonance spectroscopy, has been explored as an alternative predictor of fracture risk in patients with AN. In the bone marrow, adipocytes and osteoblasts are derived from a common progenitor, the mesenchymal stem cell. In AN, these common progenitors are more likely to produce adipocytes than osteoblasts [24], leading to increased bone marrow adiposity which impairs bone resistance to mechanical stress [25]. In fact, patients with AN have been found to have increased bone marrow fat fraction at the femoral neck and vertebral bodies [20, 26], and a negative correlation has been described between bone marrow fat and total hip BMD [26]. In addition, higher bone marrow fat has been noted in patients with AN and a positive lifetime history of fractures compared to those with no fractures [20]. While bone marrow adiposity presents a promising approach toward fracture risk prediction in these patients, it should be noted that the relationship between bone marrow fat and BMD in adolescents and children is more complex [27]. In adolescents with AN, a positive correlation between marrow adiposity and BMD was seen at a younger age (close to 12 years), while a negative correlation was noted at an older age (close to 19 years) [28], possibly a result of the hormonally mediated marrow conversion (from red/hematopoietic to yellow/adipose) that occurs with puberty [29].

Factors Implicated in AN-Related Bone Disease

Several metabolic and physiological alterations have been described in patients with AN, with correlations or potential causal contributions to the observed bone mineral deficit and increased fracture risk.

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BMI, Muscle Mass, Fat Mass, and Leptin

Patients with AN have a body weight that is less than minimally expected, and a BMI that ranges from ≥ 17 kg/m^2 with mild AN, to < 15 kg/m^2 with severe disease [30]. A lower BMI in these patients is associated with lower BMD [5, 31] and BMD is inversely related to the duration of time that the patient has low BMI [1, 10]. Additionally, the lowest lifetime BMI in patients with AN seems to predict their risk of osteoporosis [32–35]. Workman et al. recently demonstrated that patients with AN-R have a lower average BMI compared to AN-BP (15.39 kg/m^2 vs 16.15 kg/m^2), and this might explain the difference in BMD between the two groups that we described in a previous section [8].

Patients with AN experience a decrease in both fat mass and lean body mass [17], and both factors have been linked to low BMD. In a study evaluating the clinical sequelae of AN in adolescent girls, lean body mass was one of the most important predictors of bone density [36] and a positive correlation had been noted between lean body mass and HR-pQCT-estimated bone strength in adolescents and young women with AN [22]. In a study of the effect of weight gain on BMD that will be discussed in a later section, Miller et al. noted that increases in lean body mass had a stronger positive effect on BMD than weight gain and fat mass gain [37]. On the other hand, patients with AN have around 14% lower fat mass than controls [3] and this is believed to result in decreased leptin concentrations [38]. Leptin concentrations in patients with AN manifest a direct correlation with BMD that is independent of BMI [33, 39]. Administration of leptin to patients with exercise-induced hypothalamic amenorrhea led to an increase in bone formation and improvement in BMD but was associated with a small degree of weight loss [40, 41]. The concern about weight loss with leptin may present a safety concern in patients with AN and this hormone has not been further investigated in this patient population.

Sex Hormones and Amenorrhea

One of the primary physiologic changes in women with AN is the central suppression of the hypothalamic-pituitary–gonadal axis, manifesting with alterations in menstrual cycles in up to 70% [14]. More specifically, the low energy state of AN is thought to cause decreased gonadotropin secretion, resulting in low amplitude luteinizing hormone (LH) pulses [42], in turn leading to decreased estrogen concentrations.

Estrogen plays an important role in bone remodeling through its well-established inhibitory effect of osteoclasts and stimulatory effects on osteoblasts [43]. The relative deficiency of this hormone in amenorrheic women with AN makes it the primary driver mediating AN-related bone disease [44]. In fact, patients with AN who remain eumenorrheic have measurably higher serum concentrations of estradiol [45] and this subset of patients have higher BMD measurements [46]. Further supporting the role played by estrogen in this context is the correlation between longer duration and earlier age of onset of amenorrhea and lower BMD measurements [10, 44, 47, 48]. This is best illustrated in women with AN who experience peripubertal onset of amenorrhea. This subgroup of patients has a 20% larger deficit in BMD compared to women who become amenorrheic after onset of puberty [44]. Because a large proportion of peak bone mass is achieved during puberty [49], a logical conclusion is that alterations of the hypothalamic-pituitary–gonadal axis during this critical period may lead to more detrimental effects on BMD and increase the risk of osteoporosis in the long-term. In interpreting these data, it should however be noted that amenorrhea in these patients is also a marker of disease severity. While a large component of the association between lower BMD and longer duration of amenorrhea may certainly be attributed to the corresponding duration and severity of estrogen deficiency, it might also be a manifestation of more severe malnutrition with its myriad additional hormonal alterations that affect bone development as we describe in the following paragraphs.

Women with AN and low BMD also have decreased testosterone concentrations [11]. Although testosterone has the ability to directly inhibit bone resorption, much of its effect is mediated by its aromatization to estrogen [49]. Therefore, it is difficult to determine the exact relationship between low testosterone and decreased BMD in women with AN. In men with AN, low testosterone concentrations correlate with lower BMD [50], but to our knowledge, no studies have investigated the effect of androgen replacement on BMD in this subset of patients.

Dehydroepiandrosterone (DHEA) and its sulfated metabolite DHEAS are another group of sex steroids that are decreased in females with AN [51–53]. In adolescent girls with AN, inverse correlations have been noted between DHEA/DHEAS the bone resorption markers [52, 53] and between DHEAS and the receptor activator of nuclear factor-κB ligand (RANKL) [53], suggesting that suppression of DHEA/DHEAS might favor bone resorption. No correlation was seen however between DHEAS and BMD or markers of bone formation [52].

Growth Hormone and IGF-1

Patients with AN have elevated growth hormone (GH) and low Insulin-like Growth Factor-1 (IGF-1), a hormone secreted by the liver in response to GH stimulation, and GH concentrations are highest in those with the lowest BMI and fat mass [54]. However, while recuperation of ~ 10% of total body weight normalizes GH, IGF-1 concentrations remain low [55]. These alterations in GH and

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IGF-1 are suggestive of both GH resistance and direct suppression of IGF-1 synthesis by malnutrition.

IGF-1 is an anabolic hormone that stimulates osteoblastic activity [56], with possible inhibitory effects on osteoclastic activity [57], raising the question of whether low IGF-1 in patients with AN may negatively impact BMD [32, 58]. Indeed, in women with AN low IGF-1 concentrations negatively predict BMD and bone microarchitectural parameters independently of BMI [39, 59].

Other Hormonal Alterations

Cortisol

The catabolic hormone cortisol is also increased in a large number of patients with AN and this is thought to be a result of chronic physiologic stress [60]. Hypercortisolemia leads to poor bone formation through inhibition of osteoblast proliferation and increases bone resorption [60, 61] and patients with AN demonstrate an inverse correlation between cortisol concentrations and BMD [33, 62]. However, it remains unclear whether hypercortisolemia is a causal factor for low BMD, or whether it is simply a marker of severe malnutrition in the disease.

Oxytocin

In animal studies, oxytocin induces osteoblast formation and inhibits osteoclast function [63]. In patients with AN, oxytocin concentrations are low [64] and normalize with weight gain [65]. Low oxytocin concentrations correlate with lower BMD independently of BMI [66]; however, there are no studies investigating the effect of oxytocin administration on bone health in patients with AN.

Parathyroid Hormone

Studies investigating PTH concentrations in individuals who have active AN have yielded contradictory results [67–69]. In a recent study that used age-specific reference ranges, a third of adolescents with AN had low PTH concentrations for age, making low PTH levels a possible contributor to low bone formation or altered bone mineralization in this group [68]. However, a study in women with AN found no alterations in PTH concentrations and no correlations between PTH and BMD were seen [69]. These finding should be interpreted with caution given the relationship between Calcium and vitamin D consumption, which may vary in patients with AN as we discuss later, and PTH.

Adipokines

In recent years, there has been increasing interest in the relationship between adipokines and bone health in patients with AN. One such cytokine secreted by adipose tissue is adiponectin, which regulates energy homeostasis through modulation of glucose and fatty acid metabolism throughout peripheral tissues [70]. Adiponectin is inversely associated with fat mass and is low in patients with obesity and type 2 diabetes [71]. However, levels of adiponectin in patients with AN have been variably reported as low, normal, or high in comparison to normal-weight controls [72–75]. Adiponectin has demonstrated an inverse correlation with bone mass in women [76] and a recent study of 80 women with AN suggested that 27% of the variance in BMD seen in these patients was explained by leptin, BMI, and total adiponectin concentrations [70]. While still unclear, there might be a role for adiponectin in bone health in patients with AN.

Peptide YY

Lastly, the enteric hormone peptide YY (PYY) may play a role in modifying bone mass and strength. PYY is a member of the neuropeptide Y family and is expressed in the brain, gastrointestinal tract, and pancreas. Systemic PYY concentrations are low during fasting states and increase with feeding [77]. Paradoxically, PYY concentrations increase in women with AN and have a strong inverse correlation with BMD at the spine [78]. Bone mineral content, bone mass, bone formation, and cortical vascularity are higher in PYY knockout mice than controls [77], and animal studies suggest that PYY inhibits osteoblastic activity while increasing osteoclastic activity [79]. Given PYY's overproduction in patients with AN, its role in bone maintenance in this population requires further investigation.

Exercise

Excessive exercise may be seen in 31–80% of patients with AN [80]. Although exercise is considered beneficial to bone health in the general population [81], it may be harmful in women with active AN who are already in a state of severe malnutrition [80]. Waugh et al. have indeed demonstrated that in women with active AN, exercising decreases BMD. However, high bone loading activities when AN is in remission—as defined by a BMI > 18 kg/m^2 with return of normal menses—lead to an increase in BMD [82].

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Can AN-Related Bone Disease be Reversed or Stabilized?

Given the growing data on the physiological and hormonal alterations that occur in individuals with AN, multiple interventions and therapeutic approaches have been proposed in order to improve bone health and some have shown promising results. It should however be noted that studies have primarily assessed treatment effects on BMD and markers of bone turnover, and that no studies have evaluated treatment effect on fracture risk. The ability to use fracture risk as an outcome has been limited by the small size of these studies and their short duration. While longer studies can improve the ability to evaluate treatment effect on fracture incidence as an outcome, the still rather low absolute number of fractures in these patients (~ 13/1000 patient-year) will require large studies and multicenter collaborations.

Weight Restoration

One of the most effective interventions to stabilize and reverse bone loss in patients with AN is weight restoration. Multiple clinical studies have investigated the link between weight restoration and changes in BMD, with many showing positive correlations [35, 47, 83–93]. In a secondary analysis of data comparing alendronate to placebo, Golden et al. compared the changes in BMD between patients who gained weight (i.e., achieved a weight at or above 85% of standard body weight) and those who did not. Patients who gained weight experienced an increase in BMD at the hip and lumbar spine that was independent of alendronate administration and resumption of menses ($r = 0.66$, $p < 0.001$) [92].

While not all studies investigating the effect of weight gain on BMD showed an increase in BMD in response to weight restoration, none observed loss of BMD with weight restoration [35, 83, 87, 89, 90, 93, 94]. At the very least, it appears that weight restoration is associated with stabilization of BMD. Additionally, many of these studies demonstrated a decline in the markers of bone turnover with weight gain which may suggest an early improvement in bone metabolism not yet reflected by measurement of BMD [83, 88, 90, 94]. One specific example is the study by Compston et al. which followed 21 young women who gained 10 kg on average over one year. No increase in BMD was observed but there was an increase in the concentrations of bone formation markers and a decrease in the concentrations of bone resorption markers, suggesting a possible positive effect of weight gain that was likely too early to capture by DXA [94].

Although some studies showed improvement of BMD with weight gain alone [86, 91, 92], others suggested that both weight restoration and resumption of menses were necessary for BMD to increase [84, 85] and at least one study showed improvement in BMD with resumption of menses that was independent of weight gain [37]. This study, which followed 45 women with AN not on oral contraceptive pills (OCP) for an average of 13.5 months, demonstrated differential effects of weight gain and restoration of menstrual function on BMD. Patients who did not experience weight gain or restoration of menstrual function sustained a decline in BMD at the lumbar spine and hip of 2.7% and 2.6%, respectively. By contrast, those who gained weight and experienced resumption of menses demonstrated an increase in BMD of 3.6% and 2.1% at the lumbar spine and hip, respectively. Analyses of the independent effects of weight gain and restoration of reproductive function on BMD showed an association between resumption of menses and improved lumbar spine BMD that was independent of weight gain, and an association between increased weight and hip BMD that was independent of restoration of reproductive function [37].

In summary, the majority of studies suggest that weight restoration is almost always necessary to stop or reverse bone loss. However, it is still not fully clear whether this beneficial effect is primarily due to increased bone loading, restoration of normal gonadal function, reversal of other hormonal abnormalities such as GH resistance, low IGF-1 or hypercortisolemia, or a combination of these factors. It is important to note that remission of the eating disorder alone may not necessarily restore BMD to normal. Many patients continue to manifest low BMD in comparison to age- and sex-matched controls even decades after remission of AN [95, 96]. In fact, in a group of women with history of AN who were able to maintain normal weight for approximately 20 years, BMD remained significantly lower compared to controls of similar weight [95]. A recent meta-analysis of studies conducted between 1996 and 2019 showed that whole-body bone mineral content in women with AN compared with healthy controls was 0.16 kg lower before and 0.1 kg lower after weight recovery [3]. These observations suggest a partially irreversible impairment of bone integrity as a result of the initial alterations seen with AN.

Calcium and Vitamin D

Calcium and vitamin D are important for bone mineralization, so it is not surprising that a large number of studies have assessed the adequacy of these micronutrient intake in patients with AN. While Hypocalcemia is not a prominent feature in patients with AN, these patients exhibit a high rate of insufficient dietary calcium consumption [97]. Among studies that evaluated vitamin D status, rates of vitamin D insufficiency and deficiency have been widely variable, ranging from about 2% to over 85% [97–102], with possible

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variations across geographic locations and by inpatient versus outpatient state. A meta-analysis of vitamin D studies in AN showed that among individuals not receiving vitamin D supplementation, concentrations of 25-hydroxyvitamin D (25-OHD) and of 1,25-dihydroxyvitamin D (1,25-OHD) were lower in patients with AN compared to controls, while no differences between the groups were seen with vitamin D supplementation [103]. While high rates of vitamin D supplementation have been reported among some patients with AN [100, 104], this behavior has not been uniformly noted in all patients [97], so attention to vitamin D supplementation is an important aspect of treatment of low BMD in patients with AN. In fact, one study on weight restoration noted the need for concomitant vitamin D sufficiency for BMD to improve [105]. Additionally, 25-OHD concentrations have been noted to decrease after weight gain in some patients [106], possibly as a result of increased fat mass and vitamin D sequestering.

Sex Hormone Replacement

Estrogen

While observational studies in adults with AN suggest improved BMD in association with OCP use [107] and oral estrogen replacement [108], clinical trials involving oral estrogen/progesterone treatment failed to show benefit [56, 109]. However, a recent open-label prospective study of transdermal estradiol (0.045 mg/day) with levonorgestrel (0.015 mg/day) in 11 women with AN showed improvement in lumbar spine and lateral spine BMD (by 2% and 3.2%, respectively) after 6 months of therapy. This was paralleled with a significant decline in bone marrow adiposity and the bone resorption marker C-terminal telopeptide (CTx) [110].

Somewhat similar findings have been observed in peripubertal patients with AN. Trials utilizing typical OCP doses in peripubertal female patients (35–50 μg of oral estradiol) for 1 and 2 years did not have any effect on BMD [37, 111–113]. In contrast, when estradiol was administered transdermally at physiologic doses (100 μg in patients with bone age > 15 years, or escalating doses of 3.75–11.25 μg orally in those with bone age < 15 years of age), BMD did increase to near normal after 18 months of treatment [114]. It is still unclear whether this large difference in treatment response is due to the route of administration of estrogen or to the medication doses used. However, the fact that both adolescent and adult patients experienced similar responses to transdermal versus oral estrogen suggests that the difference in effect is more likely due to the route of administration. Further supporting this notion is the fact oral estrogen is hepatically metabolized and may inhibit IGF-1 and increase IGF binding protein 3 (IGF-BP3) production, thus limiting the availability of free IGF-1 [115]. By contrast, transdermal administration of estrogen bypasses the liver and the resulting effect on IGF-1. This may carry important clinical implications in the context of AN, given the low baseline IGF-1 production in these patients and its potential negative skeletal effects.

Androgens

In a study of 33 women with AN and low testosterone concentrations treated with transdermal testosterone patches for 3 weeks (150 or 300 μg), there was an increase in the bone resorption marker CTx but no changes in the bone formation markers osteocalcin and bone-specific alkaline phosphatase (BSAP) [116]. A subsequent trial randomized 19 women to testosterone alone (150–300 μg daily transdermal patch based on serum testosterone concentration), 20 to risedronate alone (35 mg/week), 20 to combination therapy with testosterone and risedronate, and 18 to placebo. After a 12-month follow-up, no improvements were found in bone turnover markers or BMD in the testosterone monotherapy or placebo groups. The only treatment groups that experienced an improvement in BMD were those that received risedronate and there was no difference between the risedronate monotherapy group and the risedronate combined with testosterone group. This suggests that testosterone supplementation is unlikely to be beneficial for treatment of osteoporosis in women with AN [117].

Treatment of women with AN with DHEA at 100 mg daily did not increase BMD compared to baseline or placebo either [118]. A clinical trial in women with AN that compared DHEA 50 mg daily to OCP (20 μg ethinyl estradiol/0.1 levonorgestrel) for one year showed no change in BMD after correction for weight gain. However, while both groups experienced a decline in the bone resorption marker N-terminal telopeptide (NTx), only patients on DHEA experienced a transient increase in bone formation markers (BASP and osteocalcin), suggesting a positive anabolic effect of DHEA [119]. Two trials comparing 18 months of DHEA in combination with OCP (DHEA 50 mg + 20 μg ethinyl estradiol/0.1 levonorgestrel) in adolescent girls and women with AN showed stabilization of BMD and improvement in DXA-derived measures of hip strength, while BMD declined in untreated controls [120, 121]. However, a third similar trial by the same investigators in adolescent girls showed a decline in BMD in the treatment group subjects who had open physes compared to placebo, while BMD remained stable in those with closed physes [122]. These results suggest a differential effect of combination therapy by bone maturity status.

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Anti-resorptive Agents

Bisphosphonates

Bisphosphonates inhibit osteoclast-driven bone resorption by impairing the formation of the osteoclast ruffled border necessary for adhesion to bone surfaces, decreasing osteoclast acid secretion necessary for bone resorption, and inducing osteoclast apoptosis [123–125]. Bisphosphonates have been widely used to treat postmenopausal osteoporosis, but few studies have systematically evaluated their efficacy in patients with AN-related bone disease. In 2005, Golden et al. conducted a randomized clinical trial on 32 adolescent females who took alendronate 10 mg daily or placebo for 1 year. The end-of-study BMD was significantly higher than baseline in the alendronate group but not in the placebo group. The magnitude of change in BMD from baseline between the two groups showed a trend in favor of alendronate that did not reach statistical significance (4.4% versus 2.3% at the femoral neck and 3.5% versus 2.2% at the lumbar spine with alendronate and placebo, respectively) [92].

Miller et al. assessed the effect of risedronate at a dose of 5 mg daily in 10 adult women with AN and osteopenia, and found a significant increase in lumbar spine BMD from baseline, by 4.1% at 6 months and 4.9% at 9 months. By contrast, a historic control group used for comparison experienced a decline in BMD at both time points, and the difference in BMD between the control and treated groups was also statistically significant. This was accompanied by an equally significant difference in the bone resorption marker NTx, with a decline in NTx in the treated group and an increase in the control group [126]. In 2011, Miller's group re-evaluated the efficacy of risedronate in a larger clinical trial with 38 women randomized to risedronate 35 mg weekly or placebo for 12 months. Compared to placebo, risedronate was associated with a 3.2% increase in BMD at the lumbar spine ($p < 0.0001$) and a 1.9% increase at the hip ($p = 0.013$) [117].

Based on these results, it is difficult to compare the efficacy of alendronate and risedronate in the treatment of AN-related bone disease. The subjects in the alendronate study were adolescents and the major bone turnover abnormality seen in this group of patients is suppression of bone formation rather than increased bone resorption. Hence, it comes as no surprise that an anti-resorptive agent might not lead to significant improvement in BMD over placebo in this setting. By contrast, the risedronate studies involved women with AN, a group with increased resorption. In this group of patients, risedronate was more effective than placebo and was accompanied by an appropriate decline in the markers of bone resorption.

Denosumab

Denosumab is a human monoclonal antibody that binds RANKL in the circulation, thus preventing activation of its target receptor (RANK) on immature osteoclasts and inhibiting bone resorption through prevention of osteoclast differentiation [127]. Its anti-resorptive action thus makes it an attractive option for treatment of AN-related osteoporosis in adult patients, where increased bone resorption has been observed. To this date however, denosumab use in patients with AN-related bone disease has only been described in case reports. Two separate reports demonstrated improvement in bone density without severe side effects. In the first report, a 29-year-old woman with AN and low BMD was treated with denosumab 60 mg every 6 months for 3 years and experienced a 14.8% increase in BMD at the lumbar spine and a 1.4% increase at the hip [128]. In the second report, three women with AN aged 36, 37, and 42 years each received denosumab for 2 years. They all experienced an increase in the BMD at the hip (ranging between 10.7 and 36.2%). Two of them experienced an increase in BMD at the lumbar spine (of 15.7% and 18.6%, respectively), while lumbar spine BMD remained stable in the third. Bone turnover markers decreased in all three patients [129]. Another more recent report used denosumab in a patient with AN and severe hyperphosphatemia after a low-trauma fracture. The patient experienced resolution of the hyperphosphatemia and after 2 years of therapy, there was a large increase in BMD at the lumbar spine and hip of 21.6% and 28.6%, respectively [130]. Lastly, a case report described the combined use of denosumab with daily teriparatide in a patient with severe AN and multiple stress fractures. After 2 years of therapy, BMD normalized at the hip, lumbar spine, and femoral neck [131]. While denosumab appears efficacious in these case studies, formal clinical trials are needed to more rigorously assess its clinical usefulness.

Anabolic Agents

Teriparatide

Teriparatide, or human recombinant parathyroid hormone 1–34, is an anabolic agent that inhibits osteoblast apoptosis [132] and enhances osteoblast function partially by increasing local secretion of IGF-1 [133, 134]. The anabolic effect of teriparatide makes it particularly attractive for the treatment of low BMD in patients with AN, which is characterized by suppressed bone formation. In a 6-month clinical trial of 21 women with AN randomized to teriparatide 20 mcg daily or placebo, patients in the teriparatide group experienced a 6.0% increase in BMD at the lateral spine after controlling for BMI, while no difference in BMD was seen at the total hip and femoral neck. The change in

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lateral lumbar spine BMD in the teriparatide group was paralleled with an increase in the bone formation marker N-terminal propeptide of type 1 procollagen (P1NP), while P1NP remained unchanged in the placebo group [135]. In a more recent study in young women with AN and severe impairment in BMD or fractures, treatment with teriparatide for 2 years led to an increase in BMD at the lumbar spine, femoral neck, and hip of 13.5%, 5%, and 4%, respectively. HR-pQCT-derived measures showed a decrease in the distal radial cortical bone density and thickness, while no changes were seen at the tibia or in trabecular bone parameters [136].

IGF-1 and GH

Since IGF-1 stimulates osteoblastic activity [137], and given that IGF-1 levels are generally decreased in patients with AN as previously described, several studies have tested the efficacy of GH or IGF-1 therapy in patients with AN-related bone disease. In comparison to age- and pubertal-matched controls with AN, adolescent females with AN treated with human recombinant IGF-1 (rhIGF-1) for 7–9 days manifested an increase in the bone formation marker P1NP and a decline in the bone resorption marker CTx [138]. In another study, concomitant administration of rhIGF-1 and OCPs for 9 months was associated with a statistically significant 1.8% increase in lumbar spine BMD, while patients who received rhIGF-1 alone showed a non-significant trend toward improvement and those who received OCP alone or none of the drugs experienced a decline in BMD. This study suggests that IGF-1 might require concomitant estrogen to instigate or augment its skeletal effect in this setting [56].

In a study of recombinant human growth hormone (rhGH), 21 adult females with AN were randomly treated with supraphysiologic doses of rhGH or placebo for 12 weeks. There was no difference in treatment-induced IGF-1 concentrations between the two groups and no difference in markers of bone turnover (P1NP, P1CP, CTx) was observed [139]. This lack of efficacy is most likely due to the GH resistance seen in these patients and that was not reversed despite supraphysiologic doses of rhGH.

Other Therapies

Menatetrenone

Vitamin K stimulates osteoblast function through carboxylation of osteocalcin [140] and menatetrenone (vitamin K2) is a vitamin K analogue that exerts similar effects. Only one non-randomized study has examined the effect of menatetrenone in women with AN. Compared to a control group that did not receive the medication ($n = 11$), patients who chose to use menatetrenone ($n = 10$) experienced a significant attenuation in the degree of bone loss at 1 year (2.8% versus 6.9% loss, respectively) [141].

Ghrelin

In vitro studies have identified ghrelin in osteoblast-like cells and its addition to cell cultures increases osteoblast-like cell proliferation and the expression of markers of osteoblast activity. When administered to rats, ghrelin was associated with increased BMD [142]. A positive correlation between ghrelin and hip BMD has been described in healthy adolescents. However, despite the elevated ghrelin concentrations in patients with AN, only weak correlations exist between ghrelin and BMD in adolescents with AN [143]. In a recent clinical trial, Fazeli et al. assessed the ghrelin receptor agonist relamorelin by randomizing 22 patients with AN to the drug or placebo for 4 weeks. Patients receiving relamorelin experienced increased weight gain and while the study did not directly evaluate impact on bone density, it noted an increase in IGF-1 levels in the relamorelin group that remained significant after adjustment for weight gain [144]. This finding may be consistent with ghrelin's known stimulatory action on GH secretion, but is still surprising to see in this group of patients given their GH resistance state. More investigation is needed to determine whether these changes in weight and IGF-1 will translate into beneficial effects on bone.

Discussion

Patients with AN often have low BMD and an elevated fracture risk. However, low BMD as measured by DXA does not consistently predict the risk of fractures in this population and more novel diagnostic approaches such as HR-pQCT and measurement of bone marrow adiposity are being evaluated to assess bone fragility in these patients. Low body weight and decreased gonadal function are probably the strongest predictors of bone mineral deficit and fracture risk. A number of other metabolic disturbances have also been described including GH resistance, decreased IGF-1 production, low leptin, low androgens, and hypercortisolemia. While these abnormalities seem to bear some correlation with low BMD, these relationships are not as strong as what is seen with low BMI and hypogonadism and causal association has not been consistently demonstrated.

Different approaches to the treatment of AN-related bone disease have been attempted, primarily in women and female adolescents. Weight gain appears to be the single most effective approach, either in isolation or combined with restoration of spontaneous gonadal function. Oral estrogen is not effective in increasing BMD, but physiologic transdermal estrogen replacement with cyclic progesterone has been

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shown to be beneficial. Evidence also suggests a potential role for bisphosphonates and for teriparatide, and isolated case reports indicate that denosumab might also be helpful.

While nutritional treatment and weight restoration remain the cornerstones of treatment for low BMD in patients with AN, potential use of pharmacotherapy should otherwise be guided by the patient's age and bone maturity since the underlying skeletal defects vary by age group. With the exception of estrogen and progesterone, none of the medications discussed in this review are approved by drug regulatory authorities for use in adolescents and young women with AN and our current knowledge lacks information on long-term safety and efficacy of these therapies. In addition, while several of the reported interventions were effective in patients with active AN, there are no data on their residual skeletal effects after treatment discontinuation, especially in patients with ongoing AN.

Finally, it is important to highlight that all studies on treatment have evaluated changes in surrogate markers of bone health, such as BMD and bone turnover markers, and that no studies measured the effect of interventions on fracture risk. While positive changes in BMD and bone turnover markers are generally interpreted as an indication of improved bone health, measurement of treatment effect on fracture risk will ultimately be necessary given the chronic nature of this disorder.

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